Section I (Amendments to the Specification)

Please replace the paragraph at page 4, lines 1-12 with the following new replacement paragraph:

Subtilisin BPN is an extracellular serine proteinase from Bacillus amyloliquefaciens having a primary translation product which is a pre-pro-protein [9,10]. A 30 amino acid pre-sequence (SEQ ID NO. [[2]]1) serves as a signal peptide for protein secretion across the membrane and is hydrolyzed by a signal peptidase [167]. The extracellular part of the maturation process involves folding of prosubtilisin, self-processing of a 77 amino acid sequence (SEQ ID NO. [[1]]2), to produce a processed complex and finally degradation of the prodomain to create the 275 amino acid (SEQ ID NO. 3) mature SBT sequence. The 77 amino acid prodomain is removed autocatalytically and it has been suggested that the prodomain delays the activation of subtilisin until after secretion from Bacillus [168] because the prodomain is a competitive inhibitor of the active subtilisin (K_i of 5.4 x 10^{-7} M) exhibiting a strong inhibition of the activity of the subtilisin.

Please replace the paragraph at page 5, lines 24-30 with the following new replacement paragraph:

In yet another aspect, the present invention comprises a prodomain protein of amino acid sequence SEQ ID NO. [[1]]2 fused to a protein of interest. Further the prodomain sequence may comprise substitutions in at least the P1-P4 amino acid residues including the following:

Prodomain	P4	P3	P2	P1
Wild-type	A	H	A	Y
Substitutions	F or Y	any	A or S	M, Y, F, H or L

Several cognate sequences have been found to be highly effective including FKAM (SEQ ID NO: 10), FKAY (SEQ ID NO: 11) or FKAF (SEQ ID NO: 12). Surprising the addition of the sequences FKAM (SEQ ID NO: 10), FKAY (SEQ ID NO: 11) or FKAF (SEQ ID NO: 12) also increase the affinity of the prodomain to the subtilisin to > 10^9 M^{-1}.

Please replace the paragraph at page 17, line 32 to page 18, line 2 with the following new replacement paragraph:

To direct a protease prodomain fusion protein of the present invention into the secretory pathway of the host cells, a secretory signal sequence (also known as a leader sequence or pre sequence) is usually required. In the present invention the prodomain sequence of the protease is part of the

fusion protein and thus secretion of the fusion protein is easily effected by including a signal sequence such as that defined in SEQ ID NO. [[2]]1.

Please replace the paragraph at page 20, line 30 to page 21, line 4 with the following new replacement paragraph:

To demonstrate the feasibility of prodomain-directed processing, a gene was constructed to direct the synthesis of a fusion of the pR8 prodomain onto the N-terminus of the 56 amino acid B domain (GB) of streptococcal Protein G. Prodomain pR8, having the mutations at amino acid residues 16-21 (QTMSTM (SEQ ID NO: 8)) which were replaced with SGIK (SEQ ID NO: 9) creating a two amino acid deletion in pR8, wherein S replaces Q16, G replaces T17, M18I replaces S19 and T20 and "K" replaces M21; along with additional substitutions A23C, K27Q, V37L, Q40C, H72K and H75K is independently stable and binds to subtilisin with- 100-times higher affinity than the wild type prodomain. Further, pR8 thus becomes the cognate sequence specifying the subtilisin cleavage site.

Please replace the paragraph at page 22, lines 2-11 with the following new replacement paragraph:

A version of pR8 was constructed with its last four amino acids (AHAY (SEQ ID NO: 13)) replaced with FRAM (SEQ ID NO: 14); denoted pR58). pR58 inhibits S160 with a K_i of ~ 30 pM. An N-terminal fusion of pR58 onto the G_B domain was found to bind to S160 with a substrate affinity (Ks) in the pM range, at least 1e5-times greater than even the highly preferred pentapeptide substrate sDFRAM-AMC. Essentially the prodomain structure acts as an amplifier of the P1 and P4 sequence signals. Hydrolysis is limited to a single turn-over by strong product inhibition. Product inhibition is difficult to avoid in using high substrate affinity to direct specific cleavage because of the structural similarity between substrate and product. We therefore do not attempt to obviate this property. As will be described later, the single turn-over reaction can be exploited in applying the system to protein purification.

Please replace the paragraph at page 25, line 8 with the following new replacement paragraph:

The prodomain of subtilisin can be replaced with a much shorter cognate sequence which has been selected for optimized binding with the processing protease. The amino acids comprising variations of only the C-terminal part of the prodomain (E E D K L (F/Y) Q S (M/L/Y) (SEQ ID NO: 7) can be used as a cognate sequence. For example, it has been shown that the IgG binding

domain of ~~Streptococcal~~ Streptococcal Protein G, which has no natural affinity to subtilisin, binds to S 194 with a sub-micromolar dissociation constant once a nine amino acid C-terminal tail has been added.